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10/526,812	08/19/2005	Jennifer Ruth Gamble	DAVI253.001APC	5804

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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
03/17/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/526,812	GAMBLE ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06-26-2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16,19-26 and 49-52* is/are pending in the application.

4a) Of the above claim(s) *20,22,24,25,26,50,51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16,19,21,23,49 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 15, 16, 19-26 and 49-52 are pending. Claims 15, 16, 19, 21, 49-51 have been amended, claims 1-14, 17, 18 and 27-48 have been cancelled and claim 52 has been added by Applicant's amendment filed on 11-24-2009. Applicants' election of the following species in the response filed on 09-11-2008 was previously acknowledged: (J) intercellular permeability, reading on claims 4 (now cancelled) and 18 (now cancelled), (L) the non-protein molecule, i.e., a small molecule antagonist, reading on claims 9 (now cancelled) and 23, and (M) Regulation of transcription, reading on claims 7 (now cancelled) and 21.
3. **Claim 20** reading on non-proteinaceous nucleic acid molecules encoding PKCζ, **claim 22** reading on non-proteinaceous agonists of the PKCζ expression product, **claim 24** reading on the protein molecule angiopoietin-1, **claim 25** reading on the non-protein molecule chelerythrine, **claim 26** reading on a mutant PKCζ, and **claims 50-51** reading on both non-elected non-protein molecules and protein molecules, were previously withdrawn from further consideration by the Examiner pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 09-11-2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. The previous office action was made FINAL by the Examiner. Please, note that the examiner of this application was previously changed and is no longer Sheridan Swope but Maria Leavitt.

5. Applicant is reminded of the right to petition under 37 CFR 1.144, if applicant disagrees with the requirements for restriction filed on 03-12-2008.

Response to Applicants' arguments in relation to restriction requirements

The following comments are provided as a courtesy to the Applicants as the restriction requirement has already been made FINAL in the previous office action, see above.

At pages 4 and 5 of the remarks filed on 06-26-2009, Applicants essentially argue that: 1) the restriction requirement mailed on March 12, 2008 does not reflect the agreement reached between Examiner Swope and Applicants' representative on February 20, 2008, particularly, in relation to species election of (M) regulation of transcription or (N) regulation of translation, 2) it was discussed that the restriction of February 20, 2008 omits small molecules antagonists that do not affect the transcription or translation of PKCζ, and instead, modulate the activity of the PKCζ expression product, 3) election of species at page 2 of the restriction requirement of March 12, 2008 includes in (D) "a small molecule antagonist", chelerythrine chloride and bisindoylmaleimide, 4) the restriction is improperly made since "a small molecule antagonist" is generic to specific "small molecules antagonists such as chelerythrine chloride and bisindoylmaleimide and 5), Applicants request the withdrawn of the finality of the restriction requirement to reflect the agreement reached on February 20, 2008. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), note that the restriction requirement and a record of the interview filed on 03-06-2008 have been recorded. Also note that Examiners with negotiation authority can provide a new, different, clear and detailed record of the restriction requirements with reasons and/or examples to support conclusions. Applicant is reminded of the right to petition under 37 CFR 1.144, if applicant disagrees with the requirements for restriction filed on 03-12-2008.

Regarding 2), as stated at page 4 of the office action filed on 12-26-2008, the elected species of non-protein small molecule antagonist can either modulate transcription, for example, by activation of the PKC promoter gene, translation of PKC, by regulating ribosomal protein levels or the PKCζ expression product by specific antibodies. Note that because the genus of "non-protein molecules" claims, i.e., claim 15, is not allowable as originally claimed, no other species will be rejoined for search and examination.

Regarding 3-5), insofar as the criteria for election practice relating to claims of genus-species, the examiner has required species election among members of the modulating agents recited in the Markush-type in claims 50 and 51 and claim 49. In contrast to Applicants' arguments, "a small molecule antagonist" is limited to a modulation agent in claim 49 and not to a genus-species claim.

Therefore, claims 15, 16, 19, 21, 23, 49 and 52 are currently under examination to which the following grounds of rejection are applicable.

Notice of Non-Compliant Amendment (37 CFR 1.121)

The amendment to the claims filed on 11-24-2009 does not comply with the requirements of 37 CFR 1.121(c) because the status of amendment claims 50 and 51 filed 11-24-2009 is not

submitted with markings to indicate the changes that have been made relative to the immediate prior version of claims 50 and 51 filed on 09-11-2008. **Claims 50-51** reading on both non-elected non-protein molecules and protein molecules, were previously withdrawn from further consideration by the Examiner pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Accordingly, claims 50 and 51 should be identified as withdrawn claims.

Amendments to the claims filed on or after 06-26-2009 must comply with 37 CFR 1.121(c) which states:

(c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. **In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression:** (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules, which include amendment of the specification and a response to the rejections set forth below. Failure to comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Withdrawn rejections in response to Applicants' arguments or amendments:

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants' cancellation of claims 2 and 7, rejection of claims 2 and 7 under 35 U.S.C. 112, second paragraph, is rendered moot.

In view of Applicants' amendment of claim 21 to recite in the alternative transcriptional or translational regulation of the PKCζ gene, rejection of claim 21 under 35 U.S.C. 112, second paragraph, has been withdrawn.

Claim Rejections - 35 USC § 102(b)

Rejection of claims **15, 16, 21, 23 and 49** under **35 U.S.C. §102(b)** as being anticipated by Hempel et al., (Circulation 1999; pp. 2523-2529; of record) has been withdrawn.

Though Hempel discloses modulation of endothelial cell intercellular permeability by exposing said cells to PKC antisense oligonucleotides, Hempel et al., does not disclose inhibiting thrombin-induced stimulation of atypical protein kinase Cζ (PKCζ), thereby down-regulating thrombin-induced vascular endothelia cell permeability.

Applicants' arguments are moot in view of the withdrawn rejection.

Claim Rejections - 35 USC § 103

Rejection of claims 15 and 19 under 35 USC 103 as being unpatentable over Hempel et al., (Circulation 1999; pp. 2523-2529) in view of Lum et al., (The Journal of Cell Biology, 1993, pp. 1491-1499; of record) has been withdrawn.

Though Hempel discloses modulation of endothelial cell intercellular permeability by exposing said cells to PKC antisense oligonucleotides, Hempel et al., does not disclose inhibiting thrombin-induced stimulation of atypical protein kinase Cζ (PKCζ), thereby down-regulating thrombin-induced vascular endothelia cell permeability.

Applicants' arguments are moot in view of the withdrawn rejection.

Objection/Rejections maintained in response to Applicants' arguments or amendments:

Claim Rejections - 35 USC § 112 – written description

Claim 15, 16, 19, 21, 23, 49 and 52 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Response to Applicants' Arguments as they relate to rejection of claims 15, 16, 19, 21, 23, 49 and 52 under 35 U.S.C. 112, first paragraph, written description

At pages 6-7 of the remarks filed on 06-26-2009, Applicants essentially argue that: 1) there is sufficient disclosure for the structure/function of the claimed genus of non-proteinaceous enhancing and/or inhibiting agents of PKCζ activity, which selectively modulate intercellular permeability of endothelial cells in a mammal so as to functionally up regulate and/or down-regulate said permeability, 2) Applicants have demonstrated that angiopoietin-1 inhibits PKCζ gene product rather than PKCζ translation or transcription, 3) The Examiner's statements regarding the alleged lack of disclosure regarding how angiopoeitin- 1 regulates the transcription of PKCζ expression product, highlights the problem with the Restriction set forth above, 4), angiopoeitin-1 is not a "non-proteinaceous PKCζ modulating agent but a protein, 5) the examiner has cited that the specification as filed discloses other inhibitors of thrombin-stimulated

permeability of endothelial cells including chelerythrine and bisindoylmaleimide, 6) the specification as filed cites antisense nucleic acids and other nuclei acids as non-proteinaceous modulation agents of PKCζ providing sufficient disclosure for the claimed genus of modulators of PKCζ activity. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), 5) and 6), the fact that non-proteinaceous molecules antagonists of PKCζ activity such as nucleic acid molecules, and proteinaceous molecules antagonists of PKCζ activity such as monoclonal antibodies, are disclosed at ¶ [0064] of the published application is not disputed. However, Applicants have not provide sufficient relevant identifying characteristics of the correlation between function and structure of the genus of claimed modulation agents of PKCζ able to selectively modulate intercellular permeability of endothelial cells in a mammal. What are the active sites recognized by any nucleic acid molecule able to modulate the claimed PKCζ activity so as to enhance and/or inhibit intercellular permeability of endothelial cells in a mammal? What modulating agents which associate with PKCζ protein or PKCζ nucleic acid are responsible for functional activation of PKCζ versus inhibition resulting in modification of cellular endothelial permeability? A "laundry list" disclosure of every possible species does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species (see MPEP 2163 [R-5] under the heading "Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement").

Regarding 2) and 4), the fact that angiopoeitin-1 is not a "non-proteinaceous PKCζ modulating agent but a protein inhibiting PKCζ gene product rather than PKCζ translation or transcription is not disputed. However, with respect to applicants' argument that, "Applicants

have demonstrated that angiopoietin-1 inhibition of PKCζ occur[s] through inhibition of PKCζ translocation and activation " is not found persuasive because it is noted that the features upon which applicant relies (i.e., angiopoietin-1 inhibition of PKCζ according to the instant specification, ¶ [0143]; example 4) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26USPQ2d 1057 (Fed. Cir. 1993). This is the case here. The claims do not recite that angiopoietin-1 inhibits thrombin-induced relocalisation and phosphorylation of protein PKCζ in endothelial cells

Regarding 3), the Examiner refers Applicants to the reasons of record and the reasons set forth in the paragraphs above.

Claim Rejections - 35 USC § 112 - enablement

Please, note that the scope of enablement has been broadened in view of Applicants' remarks, in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art at the time of filing the present application, and further, in view of reconsideration of search under different premises.

Claim 15, 16, 19, 21, 23, 49 and 52 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of selectively reducing or preventing thrombin-induced vascular endothelial cell intercellular permeability in a mammal comprising contacting vascular endothelial cells with angiopietin-1, thereby inhibiting thrombin-induced stimulation of atypical protein kinase Cζ (PKCζ), thereby down-regulating thrombin-induced vascular endothelia cell permeability,

does not reasonably provide enablement for claims directed to any proteinaceous and non-proteinaceous modulation agent which associates with PKCζ protein or PKCζ nucleic acid molecule. Moreover, the claims do not reasonably provide enablement for any type of induced endothelial cell intercellular permeability other than thrombin-induced endothelial cell intercellular permeability.

The Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

Response to Applicants' Arguments as they relate to rejection of claims 15, 16, 19, 21, 23, 49 and 52 under 35 U.S.C. 112, first paragraph

At pages 6-7 of the remarks filed on 06-26-2009, Applicants essentially argue that: 1) the specification discloses exemplary inhibitors of thrombin-stimulated permeability of endothelial cells such as chelerythrine chloride, bisindolylmaleimide I and angiopoeitin-1, 2) Applicants' description, including the working examples, provide sufficient guidance regarding how to determine whether and how to modulate endothelial intercellular permeability by modulating the functional activity of protein PKCζ , by contacting the endothelial cell with a proteinaceous or non-proteinaceous modulation agent, and 3) Specifically, endothelial permeability assays are described in paragraphs [0135] and [140]-[145] providing detailed protocols that can be used to determine whether a modulation agent functions to modulate PKCζ functional activity and endothelial cell permeability. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), 2) and 3), the fact that the specification discloses how specific PKC inhibitors: chelerythrine chloride, (e.g., inhibits all PKC isoforms), calphostin C (e.g., an inhibitor of classic and novel PKC) and bisindolylmaleimide I (e.g., a concentration-dependent inhibitor of PKCs) selectively block thrombin-stimulated permeability increases in endothelial cells is not disputed. These specific PKC inhibitors are used as the starting point in the invention to determine concentrations and specifities of these specific PKC inhibitors on both thrombin-stimulated permeability and activation of PKCζ isoform. For example, Figures 1d and 1a of the specification as filed illustrate that Calphostin C and bisindolylmaleimide I at 100 nM had no effect on the thrombin-induced increases of endothelial cell permeability. Indeed, bisindolylmaleimide I only inhibits thrombin-stimulated permeability and activation of PKCζ at high concentrations of 6 μM as evidenced in Figures 1a and 4d, respectively. Note that the protein kinase C (PKC) family consists of at least 12 isoforms that possess distinct differences in structure, substrate requirement, expression and localization and, to date, identification of the physiological function of individual PKC isoforms has been restricted by the availability of few agents that inhibit or activate the isoforms with specificity (Way et al., 2000, Review, Trends in Pharmacological Sciences, pp. 181-187, Abstract). Also note that the instant claims broadly embrace any factor inducing endothelial cell permeability including α-thrombin, endotoxin, disseminated intravascular coagulation, and others. As the skilled artisan would have to extensively test many non-proteinaceous modulating agents which associate with PKCζ protein or PKCζ nucleic acid molecule (e.g. inhibitory and/or activating non-proteinaceous agents) by contacting said non-proteinaceous modulating agents with endothelial cells so as to selectively up regulate/down regulate PKCζ activity resulting in up regulation/down regulation of

endothelial cell intercellular permeability in a mammal, it would have required undue experimentation to practice the instant invention as it is claimed in its current scope.

New grounds of rejection

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 49 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. **This is a new rejection necessitated by amendment of the claims in the response filed 11/24/2009.**

Claim 49 which depends on claim 15 recites "said endothelia cell activity". However, claim 15 only refers to a "endothelial cell intercellular permeability". Thus there is not a proper antecedent bases for said endothelia cell activity in claim 15. As such, the metes and bounds of the claims cannot be determined.

Conclusion

Claims 15, 16, 19, 21, 23, 49 and 52 are not allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633